Endoplasmic Reticulum-Activated C/EBP Homologous Protein Mediates the Palmitate-Enriched Diet Induced Increase in the Lipogenic Expression in the Liver (Poster)

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Non-alcoholic fatty liver disease (NAFLD) is a wide spectrum pathophysiological disorder characterized by insulin resistance, hepatic steatosis, and inflammation. Diets rich in saturated fat are known to evoke insulin resistance, ER stress, and de novo lipogenesis and thereby contribute to the pathogenic mechanisms involved in NAFLD. Palmitic acid (palmitate) is the most abundant saturated fatty acid in the diet and palmitate-enriched diets are known to cause NAFLD in a multitude of rodent models of NAFLD. Palmitate-enriched diets are known to induce steatosis by inducing the expression of genes involved in de novo lipogenesis. However, the signaling mechanisms and the downstream molecular mediators involved have not been elucidated. In this study, we explored the role of palmitate-induced ER stress and subsequent induction of C/EBP Homologous Protein (CHOP) expression in the modulation of expression and transcriptional activities of Liver X Receptor alpha (LXRα) and Sterol Response Element Binding Protein 1c (SREBP1c), two indispensable transcription factors and master regulators of genes involved in de novo lipogenesis. We demonstrate, in exogenous palmitate-treated HepG2 cells and in the livers of palmitate-enriched diet-fed mice, that palmitate evokes ER stress leading to the induction of CHOP expression. We further show that CHOP mediates the up-regulation in expression levels and transcriptional activities of LXRα and SREBP1c. Our study identifies a unique ER stress-CHOP-LXRα/SREBP1c signaling pathway that mediates palmitate-induced up-regulation of lipogenic gene expression in the liver that may play a critical role in the etiopathogenesis of NAFLD.